
Obesity, Serum Prostate Specific Antigen and Prostate Size: Implications for Prostate Cancer Detection

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Purpose: Obesity has been associated with lower serum testosterone, theoretically resulting in decreased PSA production. Obesity has also been associated with prostatic enlargement, making the detection of existent cancer more difficult. Together these findings would result in an apparent protective effect of obesity on prostate cancer risk due to technical detection issues unrelated to cancer biology. We examined the association between BMI, and PSA and prostate weight in a cohort of men undergoing RP.

Materials and Methods: We evaluated the association of BMI with prostate weight and PSA using linear regression, adjusting for patient age at RP, year of RP, race, and pathological stage and grade in 1,414 men treated with RP between 1988 and 2004 at the 5 equal access medical centers that comprise the Shared Equal Access Regional Cancer Hospital Database.

Results: On multivariate analysis increasing BMI was associated with increasing prostate weight but only in men younger than 63 years and not in men 63 years or older (p-trend <0.001 and 0.44, respectively). In men younger than 63 years mean multivariate adjusted prostate weight \pm SE in those with a BMI of less than 25 vs 30 to 34.9 kg/m² was 33.8 \pm 1.4 vs 41.4 \pm 1.6 gm. There was no significant association between BMI and preoperative PSA (p-trend = 0.70).

Conclusions: In a cohort of men undergoing RP obesity was associated with larger prostate size but only in younger men. There was no association between BMI and PSA. Assuming equal PSA, the degree of prostatic enlargement observed in younger obese men in this study would be expected to result in a modest decrease in the odds of detecting prostate cancer in a contemporary series of PSA screened men due to the decreased sensitivity of cancer detection related to larger prostate size. Obesity may appear protective for prostate cancer in younger men due to technical issues unrelated to cancer biology.

Key Words: prostate, prostatic neoplasms, prostatectomy, obesity, prostate-specific antigen

More than 30% of adults in the United States are obese.¹ Obesity has been linked to several types of cancer, including postmenopausal breast and colon

cancers.² The relationship between obesity and prostate cancer is less clear. While several large studies showed that increased BMI was associated with an increased risk of being diagnosed with prostate cancer,^{3,4} others indicated no association.^{5,6} Interestingly a recent study using prospectively collected data from the Health Professionals Followup Study demonstrated that men with an increased BMI were less likely to be diagnosed with prostate cancer but only those younger than 60 years or those with a family history.⁷

Today most prostate cancers are detected on biopsy following an abnormal PSA test. Therefore, factors that alter PSA can affect prostate cancer detection. PSA production is under androgenic control and conditions that result in lower androgenic activity, eg obesity, could lower PSA. However, obesity is also associated with larger prostate size, suggesting that obesity may increase PSA.^{8,9} PSA and prostate volume can influence the detectability of prostate cancer in men undergoing prostate cancer screening. Therefore, if obesity were associated with altered PSA and prostatic enlargement, obesity could have a dramatic impact on cancer detection rates due to technical issues unrelated to cancer biology. Using the SEARCH Database we tested the hypoth-

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Study received Institutional Review Board approval at each institution.

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Views, opinions and endorsements are those of the authors.

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TABLE 1. *Clinical and pathological features in men undergoing RP*

	Normal Wt	Overwt	Mildly Obese	Moderately + Severely Obese	p Value
No. patients	397	684	245	88	
Median yr surgery	1997	1999	1998	2000	<0.001 (ANOVA)
No. race (%):					0.08 (chi-square test)
White	247 (63)	405 (60)	146 (60)	54 (62)	
Black	97 (25)	190 (28)	79 (32)	29 (33)	
Other	49 (12)	84 (12)	20 (8)	5 (5)	
Mean age \pm SD	62.7 \pm 7.2	62.0 \pm 6.5	61.3 \pm 6.4	59.9 \pm 6.0	0.001 (ANOVA)
PSA (ng/ml):					0.61 (ANOVA)
Median	6.8	6.9	6.8	6.0	
Mean \pm SD	9.1 \pm 7.6	8.9 \pm 7.7	9.6 \pm 11.4	8.4 \pm 8.5	
No. biopsy Gleason sum (%):					0.03 (chi-square test)
2-6	301 (78)	459 (69)	174 (73)	59 (67)	
7	59 (15)	158 (24)	51 (22)	21 (24)	
8-10	26 (7)	49 (7)	12 (5)	8 (9)	
No. clinical stage (%):					0.06 (chi-square test)
T1	164 (43)	332 (49)	121 (50)	47 (56)	
T2/T3	220 (57)	341 (51)	120 (50)	37 (44)	
RP specimen weight (gm):					0.22 (ANOVA)
Median	36	39.2	40	39.5	
Mean \pm SD	42.2 \pm 22.1	44.3 \pm 23.5	45.7 \pm 23.6	42.7 \pm 17.3	
No. pathological Gleason sum (%):					0.06 (ANOVA)
2-6	238 (63)	366 (54)	128 (53)	43 (49)	
7	111 (30)	250 (37)	87 (36)	35 (40)	
8-10	27 (7)	57 (8)	26 (11)	9 (10)	
No. pos surgical margins (%)	117 (30)	206 (30)	86 (35)	45 (51)	0.001 (chi-square test)
No. extraprostatic extension (%)	92 (23)	141 (21)	61 (25)	28 (32)	0.09 (chi-square test)
No. seminal vesicle invasion (%)	32 (8)	45 (7)	23 (9)	9 (10)	0.25 (chi-square test)
No. lymph node metastasis (%)	6 (2)	12 (2)	1 (1)	0	0.30 (chi-square test)

Normal weight—less than 25, overweight—25 or greater to less than 30, mildly obese—30 or less to less than 35, and moderately and severely obese—35 kg/m² or greater.

esis that obesity is associated with lower PSA and larger prostate size in men undergoing RP.¹⁰

MATERIALS AND METHODS

Study population. After obtaining Institutional Review Board approval at each institution data on patients treated with RP from 1988 to 2004 at Veterans Affairs Medical Centers in West Los Angeles, Palo Alto and San Francisco, California and Augusta, Georgia, and at San Diego Naval Hospital, San Diego, California were combined into the SEARCH database.¹⁰ This database includes information on patient age at surgery, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, preoperative PSA, surgical specimen pathology (specimen weight, tumor grade, stage and surgical margin status) and followup PSA data for a mean of 46 months (median 34, range 1 to 187). BMI was calculated as weight in kg divided by height in m² (kg/m²).

Patients treated with preoperative androgen deprivation or radiation therapy were excluded. Of the 2,076 patients in the SEARCH Database 401 were missing data on RP specimen weight and they were excluded. The 241 men with missing BMI data and the 20 diagnosed using a transurethral resection specimen (clinical stage T1a/T1b) were excluded, resulting in a study population of 1,414.

Prostatectomy specimens were sectioned according to the protocol at each institution.¹⁰ At all institutions prostate weight was determined by measuring the gross weight of the entire RP specimen, including the seminal vesicles and vasal tips. Prostate cancer volume was not recorded.

Statistical analysis. We used multivariate linear regression to examine the association between BMI and the outcome variables of prostate weight and PSA. BMI in kg/m² was entered as a series of indicator variables for the cate-

gories less than 25, 25 to 29.9, 30 to 34.9 and 35 or greater. PSA and prostate weight were entered as continuous terms after logarithmic transformation. We mutually adjusted for age at RP (5-year intervals), year of surgery (3-year intervals), race (black, nonblack-nonwhite vs white), pathological Gleason sum (2 to 6, 7 and 8 to 10), extraprostatic extension, seminal vesicle invasion and lymph node metastasis. To adjust for case mix among the centers we included a categorical term for each center. We tested for trend by entering the median BMI of each category as a continuous term, for which the coefficient was evaluated by the Wald test.

We tested for interactions between BMI and race (black vs nonblack), age (younger than vs the median of 63 years or older) and year of surgery (less than vs the median of 1999 or greater). For the interaction model we entered the median BMI of each category as a continuous term along with the binary variable (race, age, or year of surgery) and their cross products, of which the coefficient was evaluated by the Wald test. Statistical significance was considered as $p < 0.05$. The distribution of all clinical and pathological variables was similar among the centers in the SEARCH database. Therefore, data from all centers were combined for analyses. All statistical analyses were performed using STATA 8.0 (Stata Corp., College Station, Texas).

RESULTS

Baseline patient characteristics. Mean BMI \pm SD was 27.6 \pm 4.6 kg/m² (median 27.0). Table 1 lists the clinicopathological characteristics of the patient population, as stratified by BMI.

BMI and prostate weight. After adjusting for multiple clinicopathological characteristics increasing BMI was significantly associated with increasing prostate weight

TABLE 2. Prostate weight and PSA by BMI

BMI (kg/m ²)	Mean Prostate Wt ± SE (gm)	Mean Preop PSA ± SE (ng/ml)
Less than 25	37.4 ± 1.2	7.2 ± 0.4
25–Less than 30	40.1 ± 0.9	7.0 ± 0.3
30–Less than 35	42.2 ± 1.4	7.3 ± 0.5
35 or Greater	40.6 ± 2.4	6.7 ± 0.9
p-Trend	0.004	0.70

Values are mutually adjusted for age, race, BMI, surgery year, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and center.

(p-trend = 0.004, table 2). As BMI increased, mean prostate weight generally increased except in men with a BMI of 35 kg/m² or greater, who had lower prostate weight than men with a BMI of 30 to 34.9 kg/m². There were no significant interactions between race or year of surgery and BMI in association with prostate weight (p-interaction = 0.29 and 0.43, respectively). However, there was an interaction between age and BMI (p-interaction = 0.06). Increasing BMI was significantly related to increasing prostate weight in men younger than 63 years but not in men 63 years or older (p-trend <0.001 and 0.44, respectively, table 3). As BMI increased in men younger than 63 years, mean prostate weight generally increased, except in men with a BMI of 35 kg/m² or greater, who had lower prostate weight than men with a BMI of 30 to 34.9 kg/m².

BMI and PSA. After adjusting for multiple clinicopathological characteristics there was no significant association between BMI and preoperative PSA (p-trend = 0.70, table 2). There were no significant interactions between race, age and year of RP and BMI in association with PSA (p-interaction = 0.13, 0.48 and 0.96, respectively).

Analysis excluding men with a high percent of cores with cancer. While PSA is associated with prostate volume, it can also be influenced by prostate cancer volume. Given that pathological prostate cancer volumes were not recorded in our patients, we used the percent of biopsy cores with cancer as a surrogate of prostate cancer volume.¹¹ To exclude the possibility that men with large prostate cancer volumes unduly influenced these results, we reanalyzed the data, excluding men with a high percent of cores with cancer (greater than 50%) or men with an insufficient number of cores obtained to adequately assess biopsy tumor volume (fewer than 4 obtained). These 416 exclusions resulted in a study population of 998 men for subset analyses. When these 418 men were excluded and after adjusting for multiple clinicopathological characteristics, higher BMI was significantly associated with larger prostate weight but similar PSA (p-trend = 0.001 and 0.65, respectively). Analogous to the entire cohort data, in this subset analysis BMI was significantly associated with increasing prostate weight in men younger than 63 years but not in men 63 years or older (p-trend = 0.001 and 0.11, respectively), although the interaction was no longer statistically significant (p-interaction = 0.23).

DISCUSSION

Obesity is associated with lower testosterone. Given that PSA production is under androgenic control, this suggests that obesity may be associated with lower PSA. Moreover,

several studies have shown that obesity is associated with prostatic enlargement.^{8,9} Combining lower PSA and larger prostate size would be anticipated to result in lower prostate cancer detection. Thus, independent of tumor biology we hypothesized that obesity may be associated with a lower sensitivity of prostate cancer detection. To address this question we examined data on men who underwent RP for early stage prostate cancer. We found that obesity was significantly associated with larger prostate size but only in men younger than 63 years, while there was no significant association between BMI and PSA. These findings suggests that, assuming equal PSA, obesity may appear to be protective for prostate cancer in younger men due to technical issues related to increased prostate size and the difficulty in finding cancer at biopsy independent of any impact that obesity may have on cancer biology.

Multiple studies have shown that obesity is a risk factor for prostatic enlargement.^{8,9} In agreement, we found that higher BMI was associated with larger prostate weight but only in younger men. Multiple serum hormones altered in obesity have been implicated in prostatic enlargement, including increased serum estrogen, insulin-like growth factor-1 and insulin.^{9,12,13} In addition, a high fat diet, which is associated with obesity, resulted in prostatic enlargement in an animal model.¹⁴ However, these growth stimuli are counteracted by the lower serum testosterone (a key prostate growth factor) in obese men. Decreased serum testosterone in men with a high BMI may partially explain why men with a BMI of 35 kg/m² or greater had a smaller prostate than men with a BMI of 30 to 34.9 kg/m², although in general prostate weight increased as BMI increased.

PSA production is under androgenic control with lower androgenic activity associated with less PSA production. Therefore, factors that lower androgenic activity, eg obesity, would be anticipated to lower PSA. Indeed, a population based study from the San Antonio study of Biomarkers of Risk showed that men with higher BMI had lower PSA.¹⁵ Other population based studies in New Zealand and Japan had similar findings.^{16,17} In the current study of men diagnosed with prostate cancer and undergoing RP there was no significant association between BMI and PSA. Differences between our findings and those of population based studies likely lie in the fact that men undergoing RP represent only a select group diagnosed with prostate cancer, which in turn represents only a subset of the general population. As such, the characteristics of men undergoing RP may not reflect the general population.

Most prostate cancers in the United States are detected through PSA screening. Population based studies suggest that obese men have lower PSA, which may bias against prostate

TABLE 3. Prostate weight by BMI and by age

BMI (kg/m ²)	Mean Prostate Wt ± SE (gm)	
	Younger Than 63	63 or Older
Less than 25	33.8 ± 1.4	41.2 ± 1.8
25–Less than 30	36.6 ± 0.9	44.0 ± 1.5
30–Less than 35	41.4 ± 1.6	43.3 ± 2.5
35 or Greater	38.0 ± 2.3	42.5 ± 4.8
p-Trend	<0.001	0.44

Values are mutually adjusted for age, race, BMI, surgery year, extraprostatic extension, seminal vesicle invasion, lymph node metastasis, and center.

cancer detection in obese men.¹⁵⁻¹⁷ However, independent of lower PSA obese men have larger prostates. Assuming an equal sized tumor, an enlarged prostate at biopsy would make cancer detection less likely. Several reports demonstrated significant inverse relationships between prostate size and cancer detection in men undergoing biopsy.^{18,19} Consequently the larger prostate size in younger obese men would be anticipated to result in lower cancer detection rates. The potential confounding that prostate size can have on the association between BMI and cancer detection is illustrated by data from the Palo Alto Veterans Affairs Hospital, in which obese men undergoing prostate biopsy were less likely to have cancer detected.²⁰ However, after adjusting for prostate size among other clinical variables obesity was actually associated with increased odds of being diagnosed with prostate cancer. Using models developed by Finne¹⁹ and Kranse¹⁸ et al to predict the risk of cancer detection in men undergoing biopsy we can estimate the risk decrease associated with the larger prostate size in younger obese men relative to younger normal weight men. The risk estimates are based on certain assumptions, namely 1) the weight of the RP specimen in the current study was equivalent to the ultrasound volume of the prostate, 2) PSA was 6 ng/ml, which is the approximate median PSA in men in the SEARCH Database who underwent RP in 2002 to 2003, 3) rectal examination and transrectal ultrasound findings were normal and 4) free PSA was 20%. With these assumptions the percent risk decrease in younger obese men due to prostate size alone for detecting prostate cancer would be 18% and 25% using the models of Finne¹⁹ and Kranse¹⁸ et al, respectively. This suggests that obesity in younger men may be associated with a modest risk decrease for detecting prostate cancer (20% to 25%) in a contemporary series of PSA screened men due to technical issues relating to prostate size alone.

Interestingly obesity was only associated with larger prostates only in younger men. This observation is potentially important, in light of recent data suggesting that obesity may be inversely associated with prostate cancer risk but only in younger men.⁷ To what degree differences in prostate size contributed to the findings of an inverse association between BMI and prostate cancer in this prior study⁷ is obviously unknown. However, given that the magnitude of risk decrease in this prior study (30% to 50%) slightly exceeds the 20% to 25% estimated risk decrease due to larger prostates in obese men in the current study, it is still possible that BMI may be inversely related to prostate cancer in certain subsets of men.

We used total RP specimen weight as a surrogate of benign prostatic size. Thus, the seminal vesicles and vasal tips were included in these measurements. However, this allowed us to accurately determine the weight of the specimen rather than rely on estimates using various imaging modalities. We did not exclude cancer volume, which was not available in our patients, from the total RP specimen weight. However, in a contemporary series of patients undergoing RP prostate cancer volumes are typically in the range of 1 to 2 cc.²¹ Thus, the impact of a 1 to 2 cc cancer on specimen weight in a 40 gm gland is probably slight, although in some men with large cancers this may have affected the results. In the current study all patients had prostate cancer and underwent surgery for the disease. By examining only men treated with RP, rather than all men with prostate cancer, we potentially introduced a selection bias related to who was treated with RP vs other treatment

modalities. Moreover, although the current findings suggest that obesity correlates with increased prostate size and similar PSA relative to those in normal weight men, further studies in men without cancer are needed to confirm this. Mean RP specimen weights in the current study are larger than in the general population,¹² which would result in our overestimating the risk decrease associated with obesity. However, mean weights in the current study are similar to those in other studies of men undergoing biopsy, suggesting that the estimated 20% to 25% risk decrease in younger men may be close to accurate.²⁰ Finally, it should be cautioned that the estimated 20% to 25% risk decrease in younger men is based on prior studies using ultrasound prostate volume in men undergoing biopsy. The current results may not be directly comparable to these prior studies. However, the point remains that obesity may be associated with a modest but real decrease in cancer detection due to enlarged prostate size, which is clinically important and should be considered in future studies of the relationship between obesity and prostate cancer risk.

CONCLUSIONS

In men undergoing RP for prostate cancer obesity was associated with larger prostate size but only in younger men. There was no association between BMI and PSA. Prior studies have shown that larger prostate size is associated with lower cancer detection rates in men undergoing prostate needle biopsy. Assuming equal PSA concentrations the degree of prostatic enlargement in younger obese men in this study would be expected to result in a modest (20% to 25%) risk decrease for detecting prostate cancer in a contemporary series of PSA screened men due to technical issues relating to larger prostate size. Obesity may appear protective for prostate cancer in younger men due to technical issues unrelated to cancer biology.

Abbreviations and Acronyms

BMI	=	body mass index
PSA	=	prostate specific antigen
RP	=	radical prostatectomy
SEARCH	=	Shared Equal Access Regional Cancer Hospital

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EDITORIAL COMMENT

In this article, the authors addressed the possible under diagnosis of prostate cancer in obese men, and, therefore,

the fact that obesity may appear to be protective due to this artifact. They found that BMI correlated modestly with mean prostate weight at prostatectomy and only in younger men with no relationship in those with BMI greater than 25. BMI did not significantly correlate with PSA ($r = 0.70$). An interesting feature was that the median year of surgery varied highly significantly across BMI strata with more obese men undergoing prostatectomy in later years, reflecting the increase in obesity in the population and changing norms for operating in such individuals during the course of the study. It would be useful to show the BMI-prostate weight correlation separately in white and black Americans. Nonetheless, this study provides reassuring data that under diagnosis by obesity, if any, is likely to be quite small.

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REPLY BY AUTHORS

In regard to whether the association between higher BMI and larger prostate among younger men was observed equally between black and white men, upon further analysis similar patterns were noted in both populations. Among older men higher BMI was not associated with greater prostate weight among white men, although there did appear to be a suggestion of an association among black men. However, the limited number of black men in these subanalyses makes interpretation of the results difficult.

More importantly, the question is whether obesity presents a barrier to prostate cancer diagnosis. Stampfer and Ma suggest that our study provides "reassuring data that under diagnosis by obesity, if any, is likely to be quite small." The issue is what is "small"? Given that obesity represents "only" 30% of the population, a 20% to 25% decreased detection among younger obese men would indeed result in a relatively small percentage of total cancers being missed. However, among obese men we would strongly suggest that 20% to 25% under detection is not small and extremely important. Moreover, it should be kept in mind that recent studies have suggested that obese men may have lower PSA values (references 14 to 16 in article),¹ which would present an additional bias against finding cancers in obese men. Together, the lower PSA values and prostatic enlargement may reduce the detection of cancer among obese men by much more than 20% to 25%. Certainly, the point that obesity may present a barrier to prostate cancer detection has important public health concerns and deserves further study.

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